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(54) Title: XANTHINE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: This invention generally relates to the derivatives of 3,6 disubstituted azabicyclo[3.1.0] hexanes. The compounds of this invention can function as muscarinic receptor antagonists, inter alia for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to a process for the preparation of the compounds of the present invention, pharmaceutical compositions containing the compounds of the present invention and the methods for treating the diseases mediated through muscarinic receptors.

XANTHINE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention generally relates to derivatives of 3,6-disubstituted
5 azabicyclo[3.1.0] hexanes.

The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors.

The invention also relates to a process for the preparation of the compounds of the
10 present invention, pharmaceutical compositions containing the compounds of the present invention and the methods for treating the diseases mediated through muscarinic receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated
15 by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. For example, the M_1 subtype is located primarily in neuronal tissues such as cerebral cortex and autonomic ganglia, the M_2 subtype is present
20 mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (Nature, 1986; 323: 411; Science, 1987; 237: 527).

A review in Current Opinions in Chemical Biology, 1999; 3: 426, as well as in
Trends in Pharmacological Sciences, 2001; 22: 409 by Eglen et. al., describe the biological
25 potentials of modulating muscarinic receptor subtypes by ligands in different disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease etc.

A review in J. Med. Chem., 2000; 43: 4333 by Christian C. Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous system and

elaborates on muscarinic receptor structure and function, pharmacology and their therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in Molecules, 2001, 6: 142.

- 5 N.J.M. Birdsall et. al. in Trends in Pharmacological Sciences, 2001; 22: 215 have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptors of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the
10 discovery of receptor subtype-selective compounds making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives
15 of atropine such as ipratropium bromide are better tolerated than parenterally administered options but most of them are not ideal anti-cholinergic bronchodilators due to lack of selectivity for muscarinic receptor sub-types. The existing compounds offer limited therapeutic benefit due to their lack of selectivity resulting in dose limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia
20 mediated by the M₂ receptor.

Annual review of Pharmacological Toxicol., 2001; 41: 691, describes the pharmacology of the lower urinary tract infections. Although anti muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these
25 agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (W.D.Steers et. al. in Curr. Opin. Invest. Drugs, 2: 268, C.R. Chapple et. al. in Urology, 55: 33), Steers WD, Barrot DM, Wein AJ, 1996, Voiding dysfunction: diagnosis classification and management. In "Adult and Pediatric Urology," ed. JY Gillenwatter, JT
30 Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstituted piperidine derivatives; WO 93/16018 and WO96/33973 are other close art references.

A report in J. Med. Chem., 2002; 44:984, describes cyclohexylmethyl piperidinyl triphenylpropioamide derivatives as selective M₃ antagonist discriminating against the other receptor subtypes.

SUMMARY OF THE INVENTION

The present invention provides 3,6-disubstituted azabicyclo[3.1.0]hexanes which function as muscarinic receptor antagonists which are useful as safe treatment of various diseases of the respiratory, urinary and gastrointestinal systems, and method for the synthesis of the compounds.

The invention also provides pharmaceutical compositions containing the compounds, and which may also contain acceptable carriers, excipients or diluents which are useful for the treatment of various diseases of respiratory, urinary and gastrointestinal systems.

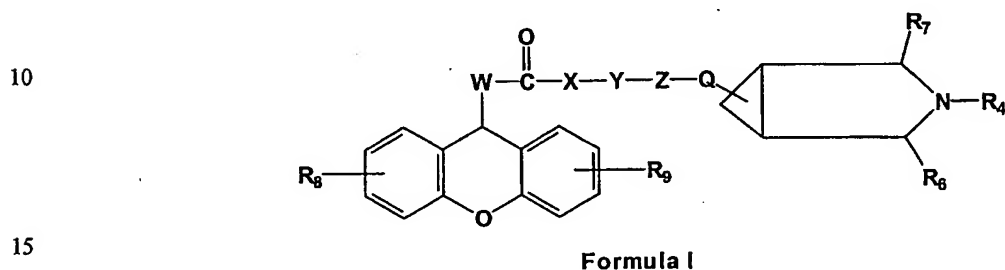
The invention also includes the enantiomers, diastereomers, polymorphs, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, N-oxides and metabolites of these compounds having the same type of activity.

The invention further includes pharmaceutical compositions comprising the compounds of the present invention, their enantiomers, diastereomers, polymorphs,

pharmaceutically acceptable solvates, esters, N-oxides or metabolites, in combination with pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows and in part will be apparent from the description or may be learnt by the practice of the invention. The objects and the advantages of the invention may be realized and obtained
5 by means of the mechanisms and combinations pointed out in the appended claims.

In accordance with one aspect of the present invention, there is provided a compound having the structure of Formula I:



and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites, wherein
20

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, -NR or no atom, wherein R represents hydrogen or C_{1-6} alkyl;

Y represents CHR_1CO , wherein R_1 represents hydrogen, methyl or $(CH_2)_q$ wherein q
25 represents 0 to 4;

Z represents oxygen, sulphur, NR_2 , wherein R_2 represents hydrogen or C_{1-6} alkyl;

Q represents $(CH_2)_n$, wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_5 wherein R_5 represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);
30

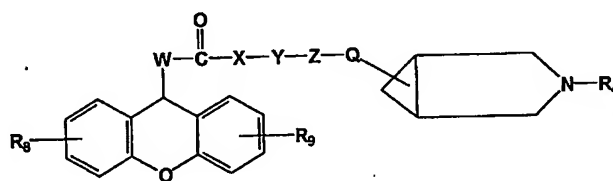
R_4 represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms
35

on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄) N,N-lower dialkylamino (C₁-C₄); N,N-lower dialkylamino carbonyl (C₁-C₄).

R₆ and R₇ are independently selected from H, COOH, CH₃, CONH₂, NH₂ or CH₂NH₂; and

R₈ and R₉ are independently selected from a group consisting of lower alkyl (C₁-C₄), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino.

In accordance with a second aspect of the present invention there is provided a compound having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein W, X, Y, Z, Q, R₄, R₈ and R₉ are the same as defined for Formula I.



Formula II

In accordance with a third aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors comprising administering to a patient in need thereof, an effective amount of compounds as described above.

In accordance with a fourth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of muscarinic receptor antagonist compounds as described above.

In accordance with a fifth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory systems such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, etc., urinary system which induce such
5 urinary disorders as urinary incontinence, lower urinary tract systems (LUTS), etc., and gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compound as described above, wherein the disease or disorder is associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of compounds as described above.

10 In accordance with a sixth aspect of the present invention, there is provided process for preparing the compounds as described above.

The compounds of the present invention exhibit significant potency in terms of their activity, which was determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetised rabbit. Compounds were tested *in vitro* and *in*
15 *vivo*. Some compounds were found to function as potent muscarinic receptor antagonists with high affinity towards M₃ receptors. Therefore, the present invention provides pharmaceutical compositions for treatment of diseases or disorders associated with muscarinic receptors. Compounds and compositions described herein can be administered orally or parenterally.

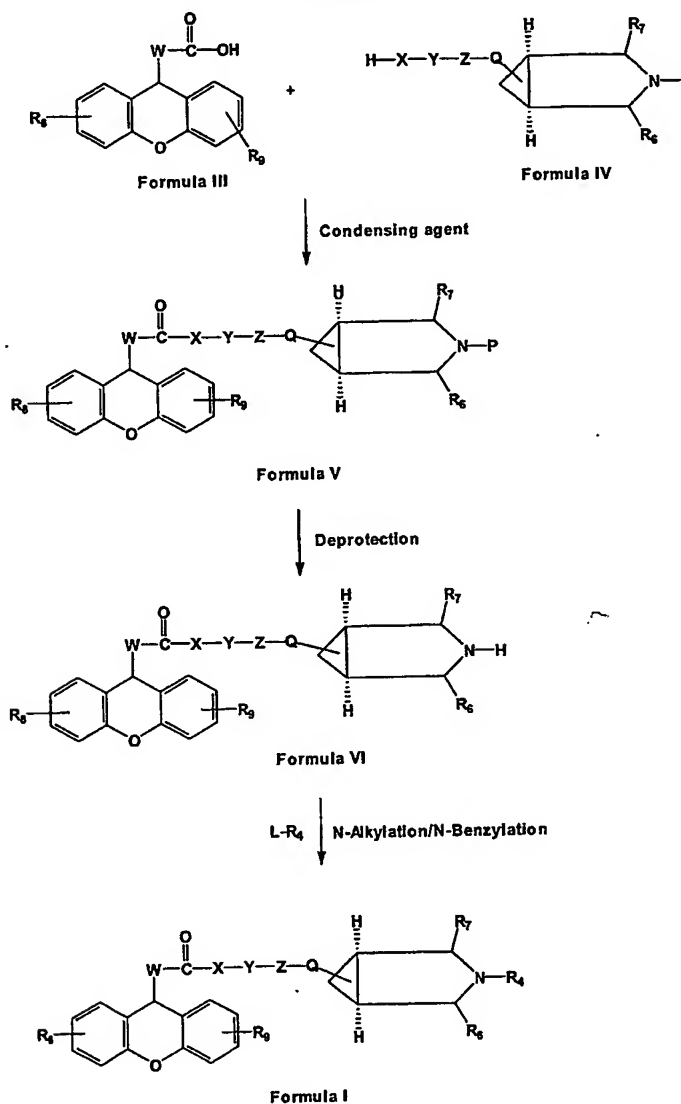
DETAILED DESCRIPTION OF THE INVENTION

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds described herein may be prepared by the following reaction sequence.

5

Scheme-I

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Although Formula I is shown with a particular stereochemical configuration, the invention is by no means limited to the production or use of compounds of a particular stereochemistry. Those of ordinary skill in the art will recognize methods for the production of compounds other than those depicted in particular Schemes or Examples,

and which are within the scope of the appended claims. The compounds of Formula I of the present invention may be prepared by the reaction sequence as shown in Scheme I. The preparation comprises condensing a compound of Formula III with the compound of Formula IV wherein

- 5 W represents $(CH_2)_p$, where p represents 0 to 1;
- X represents an oxygen, sulphur, -NR or no atom, wherein R represents hydrogen and C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen, methyl or $(CH_2)_q$ wherein q represents 0 to 4;
- 10 Z represents oxygen, sulphur, NR_2 , wherein R_2 represents hydrogen or C_{1-6} alkyl;
- Q represents $(CH_2)_n$, wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_5 wherein R_5 represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);
- 15 R_6 and R_7 are independently selected from H, COOH, CH_3 , $CONH_2$, NH_2 or CH_2NH_2 ;
- R_8 and R_9 are independently selected from a group consisting of hydrogen, lower alkyl (C_1-C_4), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C_1-C_4), amino or lower alkylamino; and
- P is any group which can be used to protect an amino group in the presence of a
20 condensing agent to give a protected compound of Formula V, which on deprotection through reaction with a deprotecting agent in an organic solvent gives an unprotected compound of Formula VI which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent $L-R_4$ to give a compound of Formula I wherein L is any leaving group;
- 25 R_4 represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms
30 on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano,

hydroxyl, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄) N,N-lower dialkylamino (C₁-C₄); N,N-lower dialkylamino carbonyl (C₁-C₄).

- 5 P is any protecting group for an amino group for a compound of Formula VI and is selected from benzyl and t-butyloxy carbonyl groups.

The reaction of the compound of Formula III with a compound of Formula IV to give a compound of Formula V can be carried out in presence of a condensing agent, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1, 8-
10 diazabicyclo [5.4.0] undec-7ene (DBU).

The reaction of the compound of Formula III with a compound of Formula IV to give a compound of Formula V can be carried out in a suitable solvent for example, N, N-dimethylformamide, dimethylsulfoxide, toluene and xylene at a temperature ranging from about 0 to about 140°C.

- 15 The deprotection of the compound of Formula V to give a compound of Formula VI can be carried out with a deprotecting agent, for example, palladium on carbon, trifluoroacetic acid (TFA) and hydrochloric acid.

The deprotection of the compound of Formula V to give a compound of Formula VI can be carried out in a suitable organic solvent, for example, methanol, ethanol,
20 tetrahydrofuran and acetonitrile at temperatures ranging from about 10 to about 50°C.

The N-alkylation or benzylation of the compound of Formula VI to give a compound of Formula I can be carried out with a suitable alkylating or benzylating agent, L- R₄ wherein L is any leaving group, known in the art, for example, halogen, O-mesityl and O-tosyl group.

- 25 The N-alkylation or benzylation of the compound of Formula VI to give a compound of Formula I can be carried out in a suitable organic solvent such as N, N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and acetonitrile, at temperatures ranging from about 25 to about 100°C.

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, etc. are mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, N-alkylating/benzylating agents, solvents, etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

Suitable salts of compounds represented by the Formula I were prepared so as to solubilize the compound in aqueous medium for biological evaluations. Examples of such salts are pharmacologically acceptable salts such as inorganic acid salts (e.g. hydrochloride, hydrobromide, sulphate, nitrate and phosphate), organic acid salts (e.g. acetate, tartarate, citrate, fumarate, maleate, toluenesulphonate and methanesulphonate). When a carboxyl group is included in the Formula I as a substituent, it may be in its alkali metal salt form (e.g. sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by the usual prior art techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

Particular compounds which are capable of being produced by the Scheme I include:

Compound No.	Chemical Name
1.	9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]amide (Compound No. 1)
2.	9H-Xanthene-9-carboxylic acid-[3-(4-cyanobenzyl)-3-azabicyclo[3.1.0]-hex-6-yl] amide (Compound No. 2)
3.	9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl-methyl] amide (Compound No.3)
4.	9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-1-yl-methyl]- amide (Compound No. 4)

Compounds or compositions may be administered to an animal for treatment orally, or by a parenteral route. Pharmaceutical compositions disclosed herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described herein and/or at least one physiologically acceptable salt addition thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be

administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The present invention also includes the enantiomers, diastereomers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts of these compounds as well as metabolites having the same type of activity. The present invention further includes pharmaceutical composition comprising the molecules of Formula I and II, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipients.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation of the preferred compound. The examples are provided to illustrate particular aspects of the disclosure should not be constrained to limit the scope of the present invention, as defined by the claims.

EXPERIMENTAL DETAILS

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane were dried using various drying reagents according to procedures well known in the literature. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument, Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

Example 1: Preparation of 9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo [3.1.0]-hex-6-yl amide (Compound No. 1)

A solution of Xanthene-9-carboxylic acid (Lancaster Synthesis, Windham NH) (0.25g, 1 eqv) and N-3-benzyl-3-azabicyclo [3.1.0] hex-6-yl-amine (0.31 g, 1.5 eqv) (procedure of T.F. Braish et. al., Synlett, 1996, 1100) in dimethylformamide was cooled to 0°C. Butanol was then added followed by the addition of N-methyl morpholine (NMM). The reaction mixture was stirred for 30 minutes at 0°C. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) was then added and the reaction mixture was again stirred for 3 hr at 0°C. It was then allowed to stir at room temperature and the

organic compound 9H-xanthene-9-carboxylic acid-(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]-amide (0.35g) was extracted with dichloromethane. The solvent dichloromethane was evaporated under reduced pressure and dried under vacuo. The organic compound was purified by column chromatography. The melting point was 217-219°C; ¹HNMR (CDCl₃): 7.39-7.32 (m, 2H), 7.30-7.07 (m, 11H), 5.20 (bs, 1H), 4.85 (s, 2H), 3.02-2.93 (m, 3H), 2.29 (d, 2H, J=6Hz), 1.28-1.26 (m, 2H); mass (m/z): 397; IR (KBR): 3296, 2788, 1684 cm⁻¹.

Example 2: Preparation of 9H-Xanthene-9-carboxylic acid-[3-(4-cyano-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]amide (Compound No. 2)

The compound 9H-xanthene-9-carboxylic acid-(3-benzyl-3-azabicyclo [3.1.0]hex-6-yl amide (3.00 mg, 1 eqv), as prepared in Example 1, was dissolved in methanol: tetrahydrofuran (80:20) (200 ml). To this reaction mixture, palladium on carbon was added and the resulting reaction mixture was stirred for 5 hours. To that mixture, acetic acid was added, followed by stirring for 4 hours. The organic compound xanthene-9-carboxylic acid-3-azabicyclo [3.1.0]-hex-6-yl amide was then filtered off and used as such without purification, which was dissolved in dimethylformamide, and potassium carbonate and potassium iodide were added. To this reaction mixture was added 4-cyano benzyl bromide and the reaction mixture was stirred overnight at room temperature. It was then diluted with water and the organic compound 9H-Xanthene-9-carboxylic-[4-(4-cyanobenzyl)-3-azabicyclo [3.1.0]-hex-6-yl]-amide was extracted with ethylacetate. Purification of this compound was done by column chromatography using silica gel (100-200 mesh). Column was eluted with (ethyl acetate : hexane) : (50 :50), (70 :30), (85 :15) to yield 150 mg of the desired compound. The melting point was 201-202°C; ¹HNMR (CDCl₃): 7.53 (d, 2H, J=8.1 Hz), 7.38-7.26 (m, 6H), 7.13-7.08 (m, 4H), 5.21 (bs, 1H), 4.85 (s, 1H), 3.54 (s, 2H), 3.00 (d, 2H, J=8.7 Hz), 2.91 (s, 1H), 2.31 (d, 2H, J=8.7 Hz), 1.31-1.25 (m, 2H); Mass (m/z) 422; IR (KBr): 3240, 2783, 2227, 1640 cm⁻¹.

Example 3: Preparation of 9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]-methyl]amide (Compound No.3)

A solution of xanthene-9-carboxylic acid (Lancaster) (0.25 g, 1 eqv.) and N-3-benzyl-3-azabicyclo [3.1.0] hex-6-yl-methyl amine (procedure of EP 0,413,455 A2) in dimethylformamide were taken and cooled to 0°C. Butanol and N-methyl morpholine

(NMM) were also added subsequently. The solution was allowed to stir for 30 minutes at 0°C. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was then added and the stirring was continued for 3 hr at 0°C. The reaction mixture was then stirred at room temperature. The reaction mixture was diluted with water and then extracted the organic compound 9H-xanthene-9-carboxylic acid-(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]amide with ethyl acetate. Evaporated ethyl acetate under reduced pressure and dried under vacuo. The purification was done by column chromatography using silica gel. Column was eluted with a mixture of ethyl acetate : hexane (10:90); Ethyl acetate : hexane (20:80); Ethyl acetate : Hexane (30:70); Ethyl acetate : Hexane (50:50); Ethyl Acetate : Hexane (65:25) to yield 80 mg of the desired product. The melting point was 181-183°C; ¹HNMR (CDCl₃) δ: 7.39 (d, 2H, J=7.6 Hz), 7.31-7.09 (m, 11H), 5.27 (bs, 1H), 4.87 (s, 1H), 3.52 (s, 2H), 3.00-2.95 (m, 2H), 2.80 (d, 2H, J=8.5 Hz), 2.23 (d, 2H, J=8.6 Hz), 1.25-1.19 (m, 1H), 1.10 (m, 2H); Mass. (m/z): 411.2.

Example 4: Preparation of 9H-Xanthene-9-carboxylic acid-[(3-benzy)-3-azabicyclo[3.1.0]-hex-1-yl-methyl]amide (Compound No. 4)

A solution of xanthene-9-carboxylic acid (Lancaster) (0.25 g, 1 eqv.) and N-3-benzyl-3-azabicyclo [3.1.0]hex-1-yl methylamine (procedure of EP 0,413, 455 A2) in dimethylformamide was cooled at 0°C. Butanol and N-methyl morpholine (NMM) were also added subsequently. The solution was allowed to stir for 30 minutes at 0°C. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was then added and the stirring was continued for 3 hr at 0°C. The reaction mixture was then stirred at room temperature. The reaction mixture was diluted with water and the organic compound (1R or 1S) 9H-xanthene-9-carboxylic acid (3-benzyl)-3-azabicyclo[3.1.0]hex-6-yl-methyl]amide was extracted with ethyl acetate. Ethyl acetate was removed under reduced pressure and the residue dried under vacuo. The purification was done by column chromatography using silica gel. Column was eluted with a mixture of ethyl acetate: hexane (5:95); (10:90); (15:85); (20:80); (30:70); (40:60) to yield 70 mg of the desired compound. The melting point was 186-188°C; ¹HNMR (CDCl₃) δ: 7.06-7.39 (m, 13H), 5.26 (bs, 1H), 4.87 (s, 1H), 3.44 (dd, 2H, J=5.7 MHz), 3.19-3.25 (m, 2H), 2.78-2.81 (m, 1H), 2.63-2.66 (m, 1H), 2.10-2.14 (m, 1H), 1.93-1.96 (m, 1H), 1.00-1.03 (m, 1H), 0.90 (m, 1H), 0.19-0.23 (m, 1H); Mass. :m/z=411.3.

Example 5: Radioligand Binding Assays

The affinity of test compounds for M₂ and M₃ muscarinic receptor subtypes was determined by [³H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya et al., (Life Sci, 1999,64(25):2351-2358) with minor modifications.

- 5 Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min.
- 10 The pellet thus obtained was resuspended in assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70°C until the time of assay.

- Ligand binding assay: The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay volume (HEPES 20 mM, pH 7.4) at 24-25°C for 3h. Non-specific binding was determined in the
- 15 presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters(Wallac). The filters were then washed with ice cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC₅₀ & K_d were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant K_i was calculated from
- 20 competitive binding studies by using Cheng & Prusoff equation (Biochem Pharmacol., (1973), 22: 3099-3108), $K_i = IC_{50} / (1 + L/K_d)$, where L is the concentration of [³H]NMS used in the particular experiment. pki is -log [K_i].

- Functional Experiments using isolated rat bladder: Animals were euthanized by overdose of thiopentone and whole bladder was isolated and removed rapidly and placed
- 25 in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KCl 2.7; CaCl₂ 1.8; MgCl₂ 0.1; NaHCO₃ 11.9; NaH₂PO₄ 0.4; Glucose 5.55 and continuously gassed with 95% O₂ and 5 % CO₂. The bladder was cut into longitudinal strips (3mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end
- 30 connected to the base of the tissue holder and the other end connected through a force displacement transducer. Each tissue was maintained at a constant basal tension of 1 g and allowed to equilibrate for 1^{1/2} hour during which the Tyrode buffer was changed every 15-20 min. At the end of equilibration period the stabilization of the tissue contractile response was assessed with 1µmol/L of Carbachol till a reproducible response is obtained.

Subsequently a cumulative concentration response curve to carbachol (10^{-9} mol/L to 3×10^{-4} mol/L) was obtained. After several washes, once the baseline was achieved, cumulative concentration response curve was obtained in presence of NCE (NCE added 20 min. prior to the second cumulative response curve).

- 5 The contractile results were expressed as % of control E max. ED50 values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pKb values were calculated by the formula $pKb = -\log [(\text{molar concentration of antagonist} / (\text{dose ratio} - 1))]$ where, dose ratio = ED50 in the presence of antagonist/ED50 in the absence of antagonist. The results of in-vitro tests are listed in Table I.

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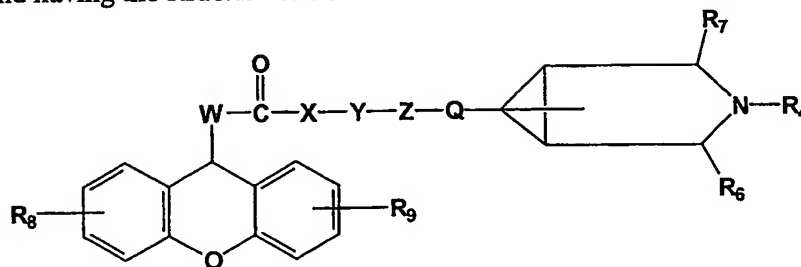
Table I

Compound No.	Receptor Binding Assay (pki)		Functional Assay (pkb)
	M ₂	M ₃	
1	<5	<5	-
2	<5	<5	-
3	6.91	7.7	8.26±0.25
4	<6	<6	-
Tolterodine	8.3	8.18	8.86±0.12

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

1. A compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein:

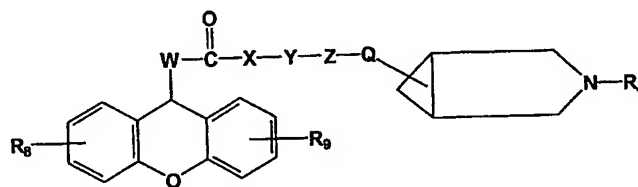
- W represents $(CH_2)_p$, where p represents 0 to 1;
- X represents an oxygen, sulphur, -NR or no atom, wherein R represent hydrogen or C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen or methyl or $(CH_2)_q$ wherein q represents 0 to 4;
- Z represents oxygen, sulphur, NR_2 , wherein R_2 represents hydrogen or C_{1-6} alkyl;
- Q represents $(CH_2)_n$ wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_5 wherein R_5 represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);
- R_4 represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxy, lower alkoxy carbonyl, halogen, lower alkoxy (C_1-C_4), lower

perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄);

R₆ and R₇ are independently selected from H, COOH, CH₃, CONH₂, NH₂ or CH₂NH₂; and

5 R₈ and R₉ are independently selected from a group consisting of hydrogen, lower alkyl (C₁-C₄), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino.

2. The compound according to claim 1 having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites wherein R₈, R₉, R₄, W, X, Y, Z, Q are the same as defined for Formula I



Formula II

15

3. A compound selected from the group consisting of

9H-Xanthene-9-carboxylic acid-(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl]amide;

9H-Xanthene-9-carboxylic acid-[3-(4-cyanobenzyl)-3-azabicyclo[3.1.0]-hex-6-yl] amide;

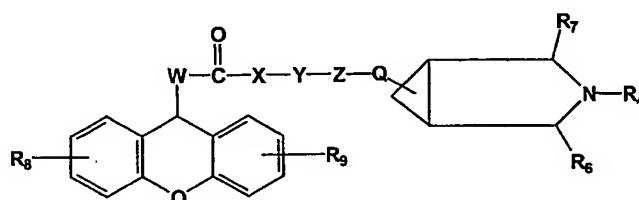
20 9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-6-yl-methyl] amide; and

9H-Xanthene-9-carboxylic acid-[(3-benzyl)-3-azabicyclo[3.1.0]-hex-1-yl-methyl]-amide.

4. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound as defined in claim 1, 2 or 3 together with pharmaceutically acceptable carriers, excipients or diluents.

25

5. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I,



Formula I

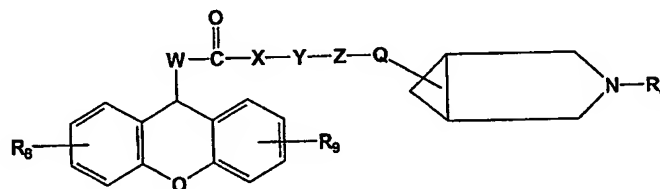
or its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein;

- W represents $(CH_2)_p$, where p represents 0 to 1;
- X represents an oxygen, sulphur, -NR or no atom, wherein R represents hydrogen or C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen or methyl or $(CH_2)_q$ wherein q represents 0 to 4;
- Z represents oxygen, sulphur, NR_2 , wherein R_2 represents hydrogen or C_{1-6} alkyl;
- Q represents $(CH_2)_n$ wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_5 wherein R_5 represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);
- R_4 represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano, hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy (C_1-C_4), lower perhaloalkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4);

R_6 and R_7 are independently selected from H, COOH, CH₃, CONH₂, NH₂ or CH₂NH₂;

R_8 and R_9 are independently selected from a group consisting of hydrogen, lower alkyl (C₁-C₄), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino.

6. The method according to claim 5 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula II, and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, polymorphs, or metabolites, wherein R_8 , R_9 , R_4 , W, X, Y, Z and Q are the same as defined for Formula I.



Formula II

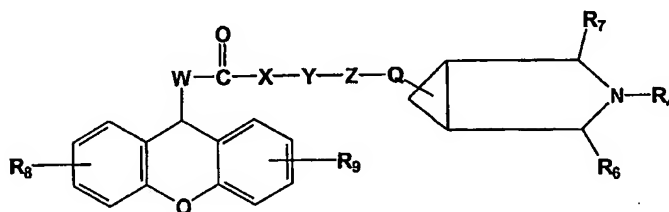
(Formula I, $R_6=R_7=H$)

7. The method according to claim 5 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkinesis.
8. The method according to claim 6 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkinesis.
9. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary, and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising

administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 4.

10. The method according to claim 9 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes, and gastrointestinal hyperkineses.

11. A process of preparing a compound of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein;

- W represents $(CH_2)_p$, where p represents 0 to 1;
- 15 X represents an oxygen, sulphur, -NR or no atom; wherein R represents hydrogen or C_{1-6} alkyl;
- Y represents CHR_1CO , wherein R_1 represents hydrogen or methyl or $(CH_2)_q$ wherein q represents 0 to 4;
- Z represents oxygen, sulphur, NR_2 , wherein R_2 represents hydrogen or C_{1-6} alkyl;
- 20 Q represents $(CH_2)_n$ wherein n represents 0 to 4, or CHR_3 wherein R_3 represents H, OH, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkoxy or CH_2CHR_5 wherein R_5 represents H, OH, lower alkyl (C_1-C_4) or lower alkoxy (C_1-C_4);
- R_4 represents hydrogen, C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon groups in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from a group consisting of nitrogen, oxygen and sulphur atoms with option that any 1 to 3 hydrogen atoms on the ring in said arylalkyl, arylalkenyl, hetero arylalkenyl group may be substituted with lower alkyl (C_1-C_4), lower perhalo alkyl (C_1-C_4), cyano,
- 25

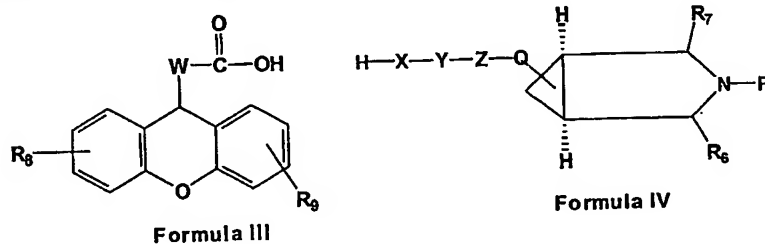
hydroxyl, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄);

R₆ and R₇ are independently selected from H, COOH, CH₃, CONH₂, NH₂ or CH₂NH₂; and

R₈ and R₉ are independently selected from a group consisting of hydrogen, lower alkyl (C₁-C₄), trifluoromethyl, cyano, halogen, hydroxy, nitro, lower alkoxy (C₁-C₄), amino or lower alkylamino, comprising

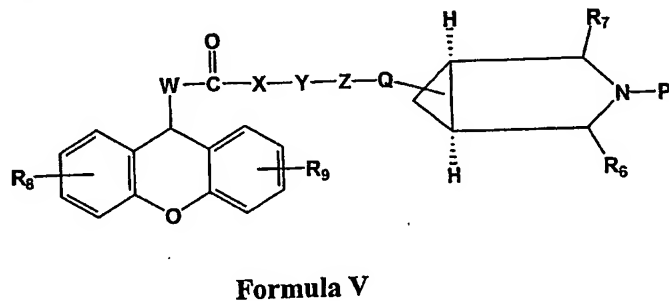
a) condensing a compound of Formula III with a compound of Formula IV

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wherein W, X, Y, Z, Q, R₇, R₆, R₉, R₈ have the same meanings as defined earlier for Formula I, to give a protected compound of Formula V, wherein P is a protecting group for an amino group,

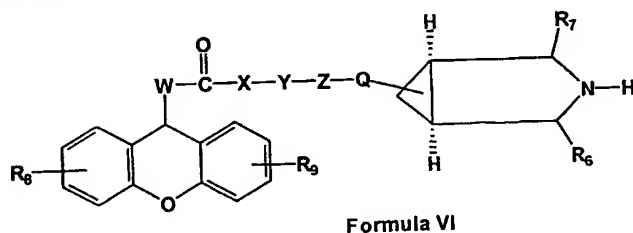
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b) deprotecting the compound of Formula V in the presence of a deprotecting agent to give an unprotected intermediate of Formula VI wherein R₆, R₇, R₈, R₉, W, X, Y, Z, Q are the same as defined earlier, and

25



- c) the intermediate of Formula VI is N-alkylated or benzylated with a suitable alkylating or benzylating agent, L-R₄ wherein L is any leaving group, to give a compound of Formula I wherein R₄, R₈, R₉, R₆, R₇, W, X, Y, Z, Q are the same as defined earlier.
- 5
12. The process according to claim 11 wherein P is selected from the group consisting of benzyloxy and t-butyloxy carbonyl groups.
13. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV to give a compound of Formula V is carried out in a suitable condensing agent which is selected from the group consisting of 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).
- 10
14. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV to give a compound of Formula V is carried out in the presence of a suitable solvent selected from the group consisting of N,N-dimethylformamide, dimethyl sulphoxide, toluene and xylene.
- 15
15. The process according to claim 11 wherein the reaction of a compound of Formula III with a compound of Formula IV is carried out at a temperature ranging from about 0-140°C.
- 20
16. The process according to claim 11 wherein the deprotection of a compound of Formula V to give a compound of Formula VI is carried out with a deprotecting agent which is selected from the group consisting of palladium on carbon, trifluoroacetic acid and hydrochloric acid.
17. The process according to claim 11 wherein the deprotection of a compound of Formula V to give a compound of Formula VI is carried out in a suitable solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran, and acetonitrile.
- 25
18. The process according to claim 11 wherein the N alkylation or benzylation of a compound of Formula VI to give a compound of Formula I is carried out with a

suitable alkylating or benzylating agent, L-R₄, wherein L is any leaving group and R₄ is the same as defined earlier.

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/IB 02/05589

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 A61K31/40 A61P11/00 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 01 04118 A (ALMIRALL PRODESFARMA S.A.) 18 January 2001 (2001-01-18) claims 1-35	1-18
A	WO 98 05292 A (SCHERING CORPORATION) 12 February 1998 (1998-02-12) claims 1-12	1-18

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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S document member of the same patent family

Date of the actual completion of the international search

10 April 2003

Date of mailing of the international search report

17/04/2003

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INTERNATIONAL SEARCH REPORT

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